Long-term safety of cilostazol in patients with peripheral artery disease: The CASTLE study (Cilostazol: A Study in Long-term Effects)

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Background: **Cilostazol, a phosphodiesterase III inhibitor, is indicated to treat the symptoms of intermittent claudication and increase walking distance in patients with peripheral arterial disease (PAD). At the time of approval, the United States Food and Drug Administration required an additional long-term safety study to evaluate the effect cilostazol on mortality.**

Methods: **A total of 1899 subjects with a clinical diagnosis of PAD and symptoms of claudication were screened for participation in a randomized, double-blinded, placebo-controlled safety study of cilostazol. The intent-to-treat (ITT) population, which was the primary analysis (n = 1435), was defined as all randomized patients who received at least one dose of study medication and included patients who were followed up >30 days after discontinuation of study drug. A total of 717 patients received cilostazol and 718 received placebo. Cilostazol was administered at a primary dose of 100 mg twice daily. The dose could be reduced to 50 mg twice daily if patients experienced an adverse event that might have been drug related.**

Results: **Long-term adherence to study medication was poor, with >60% of participants discontinuing therapy by 36 months. The mortality analysis therefore focused on deaths during the period on-treatment, defined as the period during which the study drug was taken plus a 30-day follow-up period after dosing. Total patient-years of exposure were 1046 on-treatment for cilostazol and 1090 for placebo. On-treatment, there were 18 deaths on cilostazol and 19 deaths on placebo for a hazard ratio of 0.99 (95% confidence interval [CI], 0.52-1.88). Cardiovascular deaths on-treatment occurred in 14 patients on cilostazol and 14 on placebo. In the full ITT population at 36 months, there were 101 deaths, 49 on cilostazol and 52 on placebo, with hazard ratio of 0.94 (95% CI, 0.64-1.39). Thus, most deaths occurred >30 days after study drug discontinuation. Serious bleeding events affected 18 patients taking cilostazol in the on-treatment population and 22 taking placebo. The rates of bleeding events were similar in patients who used aspirin, aspirin plus clopidogrel, or anticoagulants at anytime during the course of the study**

Conclusions: **This long-term study demonstrated no safety signal for cilostazol on all-cause or cardiovascular mortality. The study, however, was underpowered to detect a small adverse impact of cilostazol on mortality (hazard ratio upper bound of the 95% CI was 1.88 in the on-treatment population). Serious bleeding events appeared not to be increased by cilostazol. (J Vasc Surg 2008;47:330-6.)**

Peripheral artery disease (PAD) is a prevalent manifestation of cardiovascular disease that is associated with significant long-term morbidity and mortality.[1,2] A variety of therapies have been developed to treat the limitation in exercise performance, community walking ability, and reduced quality of life associated with claudication, the major symptomatic manifestation of PAD.[3]

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Cilostazol was approved by the United States Food and Drug Administration (FDA) to treat the symptom of claudication on the basis of an extensive efficacy database substantiating treatment benefit on improvements in peak exercise performance and quality of life in patients with claudication.[4,5] Cilostazol, however, is a member of the phosphodiesterase-III drug class, and other drugs from this class have been associated with excess mortality when used in patients with heart failure. An example is the long-term administration of milrinone for the treatment of heart failure, which was associated with a statistically significant 28% increase in all-cause mortality.[6]

Although the randomized trials evaluating the efficacy of cilostazol in patients with claudication did not suggest an increased risk, a total of only 16 deaths occurred in the entire safety data base of 2702 patients followed up to 6 months.[7] Despite the balance in these events between drug and placebo, the few number of deaths could not exclude more than a twofold increased mortality risk in the patients evaluated for efficacy.[8] Therefore at the time of approval, the FDA required an additional long-term safety study of cilostazol.[9]

Because of these considerations, a randomized, placebo-controlled study was initiated to evaluate the long-term safety of cilostazol in patients with PAD. The CASTLE (Cilostazol: A Study in Long-term Effects) study had a primary objective to evaluate all-cause mortality, with secondary aims to evaluate cardiovascular mortality as well as the tolerability of cilostazol in patients followed up for approximately 3 years. This study tested the hypothesis that all cause mortality would be similar between patients randomized to cilostazol compared with placebo.

METHODS

Study design and management. This was a phase 4 (postmarketing) multicenter, randomized, double-blind, placebo-controlled, parallel-arm study comparing the effects of cilostazol vs placebo in patients with claudication secondary to PAD. All sites obtained institutional review board approval of the protocol, and patients signed informed consent before their participation (Appendix, online only). Patients who met inclusion/exclusion criteria underwent a 30-day single-blind placebo run-in phase. Subjects who failed to comply with at least 70% of their prescribed regimen were withdrawn from the study. The remaining subjects had a measurement of their ankle-brachial index (ABI) and were randomized.

Patients were followed up to 3.5 years and were seen in the office every 26 weeks. Additional assessments were made by telephone every 13 weeks interspersed between the office visits. If the patient prematurely discontinued the study medication, telephone assessments were made every 13 weeks to evaluate the patient for mortality until the conclusion of the study.

The study was managed by Pharmaceutical Products Development, Inc, Morrisville, North Carolina. This included site monitoring of 100% of the source documents, data management, and statistical analysis.

Inclusion/exclusion criteria. Inclusion criteria included subjects aged ≥17 years old with a history of intermittent claudication secondary to PAD as diagnosed by a physician (specific ABI criteria for inclusion were not defined). Patients taking aspirin, clopidogrel, pentoxifylline, or anticoagulants were eligible for participation. Exclusion criteria included women who were pregnant or breastfeeding, patients currently or previously using of cilostazol, use of an investigational drug in the past 30 days, consumption of grapefruit juice, or patients found to be noncompliant during the 30-day single-blind, run-in phase. Patients with current congestive heart failure of any severity, as assessed by the site investigator, were excluded, but those with a history of heart failure who had recovered were eligible for enrollment.

Dosing. The study drug or matching placebo was administered orally as two 50-mg tablets twice a day (total daily dose, 200 mg) at least 30 minutes before or 2 hours after breakfast and dinner. Patients could reduce their dose to 1 tablet (50 mg of cilostazol or placebo) twice a day if they experienced an adverse event that in the view of the investigator was drug-related and there was concern for continued participation in the study. The reduced dose (1 tablet twice a day) could also be administered in patients taking medications that inhibited cytochrome P-450 isoenzymes 3A4 or 2C19, or both, determined by the judgment of the site investigator. In the patients randomized to placebo, 16% decreased their dose to 1 tablet twice a day and in those randomized to drug, 15% decreased their dose to 50 mg twice a day. Compliance with medication was assessed with pill counts at each follow-up visit.

At the end of the placebo run-in, median compliance was 96.0% in the overall population. Six months after randomization, median compliance was 95% on cilostazol and 96% on placebo. At the final study visit (or early termination), median compliance was 93% on drug and 94% on placebo. Thus, the patients analyzed on-treatment had a high degree of drug compliance (using the pill count method) during the treatment period.

Because the primary intent of this study was to evaluate safety, a data monitoring committee was retained to oversee the conduct and safety of the trial.

Definition of outcome events. After completion of the trial and the protocol-specified analyses, the sponsor formed a Publications Committee (Drs. Hiatt, Money, and Brass) to disseminate the results. Dr Money was the principal investigator for one of the study sites. Dr Hiatt was a subprincipal investigator for the Colorado site, but Dr Brass had no involvement with the study until after its completion. The committee had full access to study data and final approval of the current manuscript.

The study's primary objective was to assess the safety of cilostazol, defined as all-cause mortality, in patients with PAD. Given the high discontinuation rate of the study medication and that most deaths occurred >30 days after discontinuation of study drug, the committee determined that the original intent-to-treat (ITT) analysis would not provide a full assessment of cilostazol safety or risk. Therefore, the committee used a primary analysis based on deaths that occurred while patients were taking the study medication plus a 30-day period designed to capture deaths that might have resulted from exposure to the study medication; hereafter, this is regarded as the "on-treatment" period. The original, prospectively defined ITT population was also evaluated and defined as all randomized patients who received at least one dose of study medication. Also tabulated were deaths occurring in the ITT population during the entire study period, including those >30 days after study medication discontinuation.

The Publication Committee reviewed all deaths to categorize those that were cardiovascular, defined as sudden death, myocardial infarction, stroke, and heart failure. This blinded, post hoc review was limited in scope because available information was from the site's adverse event narrative. These narratives were obtained from the case report forms from the sites. Assignment of a death as cardiovascular was done by the majority opinion after independent review by the committee members.

Definition of adverse events. Adverse and serious adverse events were reported on a descriptive basis by

categorization of the event by the study sponsor according to standard definitions from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines.[10] All adverse events were recorded when patients were on-treatment through 14 days after discontinuation of treatment. Nonfatal adverse events were not monitored after drug discontinuation. Serious adverse bleeding events were defined as hemorrhages that were fatal, life-threatening, required or prolonged hospitalization, caused significant disability, or were medically significant in the judgment of the site investigator. As noted, patients were monitored for up to 42 months to ascertain mortal events.

Serious adverse bleeding events were further categorized in the subgroups of patients who were also noted to be taking aspirin, clopidogrel, or anticoagulants (warfarin or heparin). However, the temporal association of the bleeding adverse event in relation to the concomitant use of an antithrombotic drug (as well as the duration of the antithrombotic therapy) could not be ascertained from the information recorded.

Sample size and change in study management. The study assumed a 4.5% annual mortality rate, which was anticipated to result in 185 deaths after a mean follow-up of 34 months. This mortality rate was based on historic data at the time the study was designed.[2,11] This would assure a 95% power to detect a 75% difference in hazard rates between the groups randomized to cilostazol or placebo at a significance level of 0.05 for a two-sided comparison. Using these estimates, a recruitment of 1434 subjects (717 per group) was projected based on a 34-month study with an accrual period of 18 months.

The first patient visit occurred on May 25, 2001, and recruitment was completed by September 2003; however, by March 22, 2004 (34 months after first randomization), there were <80 deaths. To achieve the protocol-specified number of deaths, it would have been necessary to continue the study for several more years. With the lower than predicted death rate and higher than predicted dropout rate, the sponsor decided that it was not feasible to continue the study until the planned number of events had occurred. On July 7, 2004, the sponsor reached agreement with the FDA to terminate the study early. The last patient visit was November 3, 2004, at a time when the study had accrued 101 deaths.

Analysis plan. Baseline demographics, risk factors, comorbid conditions, and medications (Table I) were compared with an unpaired *t* test. Analyses of the primary outcomes were performed on the ITT population, which was defined as all randomized patients who received at least one dose of drug. The primary analysis (specified post hoc) was limited to the on-treatment period defined as the period during which the patient took study medication plus a 30-day follow-up period. This was a time to event analysis for all-cause mortality, and survival curves were generated using Kaplan-Meier product limit estimates, and the treatment groups were compared using a log-rank test. The null hypothesis that the relative mortality hazard ratio of cilostazol to placebo is 1.0 (ie, that the hazards are equal in the two groups) was tested at the $P = .05$ level (two-sided) using the log-rank statistic. The 95% confidence interval (CI) for the hazard ratio was provided from the Cox proportional hazards regression model. No covariate or prognostic factor was used in the primary analysis. Secondary analyses were conducted on the full ITT population using the same methods (this was the primary analysis in the original protocol).

Table I. Baseline demographics of all randomized patients in the intention-to-treat population

Characteristics	*Cilostazol*	*Placebo*	*P*
Demographics			
Number	717	718	
Age, years ± SD	66.5 ± 10.2	65.9 ± 10.5	.215
Sex (male), No (%)	470 (65.6)	470 (65.5)	.998
Race, No (%)			
Non-Hispanic white	566 (78.9)	570 (79.4)	.857
Black	116 (16.2)	117 (16.3)	
Hispanic	30 (4.2)	24 (3.3)	
Other	5 (0.7)	7 (1.0)	
Weight, kg ± SD	84.6 ± 19.5	84.6 ± 18.8	.985
Ankle-brachial index*	0.74 ± 0.23	0.76 ± 0.24	
Risk factors, No. (%)			
Cigarette smoking			
Never	106 (14.8)	99 (13.8)	.488
Former	406 (56.6)	394 (54.9)	
Currently	205 (28.6)	225 (31.3)	
Diabetes	271 (37.8)	242 (33.7)	
Hypertension	591 (82.4)	582 (81.1)	
Hypercholesterolemia	588 (82.0)	560 (78.0)	
Comorbid conditions, No. (%)			
Myocardial infarction	210 (29.3)	208 (28.9)	
Stroke	74 (10.3)	76 (10.6)	
Congestive heart failure	34 (4.7)	35 (4.9)	
Medications at baseline, No. (%)			
Aspirin	526 (73.4)	504 (70.2)	
Clopidogrel	195 (27.2)	198 (27.6)	
Warfarin	86 (12.0)	92 (12.8)	
Statins	506 (70.6)	509 (70.9)	

*Excludes 7 patients with an ankle-brachial index >1.40 at baseline.

RESULTS

The study screened 1899 subjects, of which 1795 entered the baseline run-in period and a final total of 1439 were randomized. Four patients, however, did not receive the study drug, so the ITT population consisted of 717 randomized to cilostazol and 718 randomized to placebo for a total of 1435 patients. By 34 months after the first patient was randomized, less than half of the projected number of deaths had occurred and the discontinuation rate from study drug was high, which led to study termination in November 2004, as already described. As a result, the study was underpowered to meet its primary end point, but inferences with respect to cilostazol effects on mortality could be described by the 95% CI of the hazard ratio.

Table II. Mortality during the on-treatment period (receiving study medication plus 30 days) and mortality during the intention-to-treat period

Mortality	*Cilostazol*	*Placebo*
All cause mortality on-treatment		
Median time, d	537	558.5
Deaths, No.	18	19
Event rate/person-year	1.72	1.74
Total patient-years exposure	1046	1090
Cardiovascular mortality on-treatment		
Deaths, No.	14	14
Event rate/person-year	1.34	1.28
All-cause mortality-ITT		
Median time, d	778	778
Deaths, No.	49	52
Event rate/100 person-years	3.31	3.50
Total patient-years exposure	1480	1486
Cardiovascular mortality-ITT		
Deaths, No.	28	33
Event rate/person-year	1.89	2.22

ITT, Intention to treat.

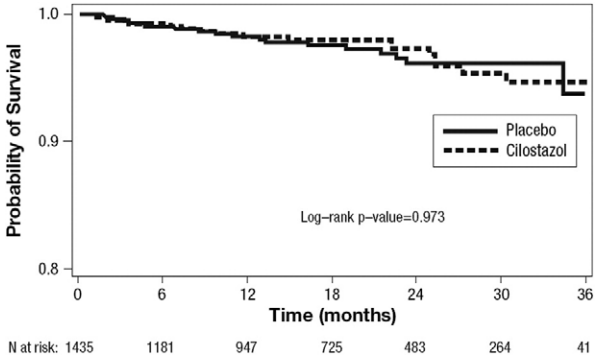

Fig. All cause mortality ≤30 days after the last dose of drug in the on-treatment population.

At baseline, randomized patients were an average age 66 years, 66% were men, and 79% were non-Hispanic white. The ABI was 0.74 ± 0.23 in patients randomized to cilostazol and 0.76 ± 0.24 in those randomized to placebo. All baseline demographics were similar between groups (Table I). The baseline prevalence of cardiovascular risk factors was also similar between groups: 86% of the patients were either current or former smokers, 36% had diabetes mellitus, almost 30% had had a prior myocardial infarction, and 10% had a history of a stroke. Although active congestive heart failure was an exclusion criterion, almost 5% of the patients enrolled had a history of congestive heart failure that was clinically resolved.

Antiplatelet use was common at baseline and equal in both groups. Aspirin was also being taken by 73% of patients randomized to cilostazol and in 70% of patients taking the placebo. Clopidogrel use was less common than aspirin, but equal in both groups. Approximately 12% of patients were taking warfarin anticoagulation. More than 70% of both groups were taking statins. Thus, most of the patients were receiving standard risk reduction therapies (antiplatelet drugs and statins).

The probability of discontinuation from the study was 68% in the cilostazol group and 64% in the placebo group at 36 months. The discontinuation hazard ratio for cilostazol compared with placebo was 1.064 (95% CI, 0.925-1.224; $P = .39$). The high dropout rate (early termination) was primarily driven by patient withdrawal of consent (16%), adverse events (18%), or other reasons (10%). The median length of drug exposure was 537 days for the cilostazol group and 558.5 days for the placebo group (Table II). This represented cumulative exposures of 1046 patient-years on cilostazol and 1090 patient-years on placebo.

At the conclusion of the study, vital status was unknown in 92 subjects (45 on cilostazol and 47 on placebo) in the ITT population. In those subjects, 78 withdrew complete consent, 13 were lost to follow-up, and one was terminated from the study by the site investigator. Only 24 patients (1.7%) were completely lost to follow-up, and of those, vital status was not known in only six patients at study termination (2 on cilostazol, 4 on placebo).

A total of 37 deaths occurred in the on-treatment population, with 18 deaths on cilostazol and 19 on placebo (Table II). This resulted in a mortality hazard ratio of 0.99 (95% CI, 0.52-1.88, $P = .97$). Fig 1 shows all-cause survival curves on cilostazol or placebo during the on-treatment period. Given that 25% of patients had an ABI >0.90, a sensitivity analysis was performed by removing those and repeating the primary analyses for the on-treatment population. In the 703 patients who had an ABI value <0.90, there were a total of 31 events. The hazard ratio for all cause mortality was 1.16 (95% CI, 0.57-2.36).

A total of 101 deaths occurred in the ITT population, including 49 on cilostazol and 52 on placebo (Table II). The all-cause mortality hazard ratio for cilostazol compared with placebo was 0.94 (95% CI, 0.64-1.39, P = .77). The hazard ratio for cardiovascular deaths was 1.054 (95% CI, 0.502-2.210; $P = .89$) in the on-treatment population and 0.852 (95% CI, 0.515-1.410; $P = .533$) in the ITT population (Table II).

Adverse events were generally balanced between groups. Table III presents the adverse events that affected >5% of either group with a ratio >1.50 between groups, serious adverse events that affected >1% of either group with a ratio >2.00 between groups, and adverse events that led to discontinuation that affected >1% of either group with a ratio >2.00 between groups. As previously described, headache was common on cilostazol, affecting 10.5% compared with 4.9% of those on placebo. Diarrhea was also common on cilostazol, affecting 10.9% of patients compared with 6.7% of patients on placebo. Palpitations were also noted numerically more often on cilostazol, and bronchitis numerically more often on placebo. Serious ad-

Table III. Selected adverse events, serious adverse events, and events leading to discontinuation

Adverse event	*Cilostazol*	*Placebo*	*Ratio*
Minor events, No (%)*			
Headache	75 (10.5)	35 (4.9)	2.14
Palpitations	38 (5.3)	18 (2.5)	2.12
Diarrhea	78 (10.9)	48 (6.7)	1.63
Bronchitis	23 (3.2)	37 (5.2)	0.62
Serious events, No (%)†			
Dyspnea	7 (1.0)	3 (0.4)	2.50
Cerebrovascular accident	7 (1.0)	15 (2.1)	0.48
Carotid artery stenosis	5 (0.7)	11 (1.5)	0.47
Femoral artery occlusion	3 (0.4)	7 (1.0)	0.40
Cardiac arrest	2 (0.3)	7 (1.0)	0.30
Events leading to discontinuation, No. (%)‡			
Edema	10 (1.4)	0 (0)	
Headache	15 (2.1)	2 (0.3)	7.00
Diarrhea	20 (2.8)	5 (0.7)	4.00

*Adverse events are reported that affected >5% of either group with a ratio >1.50 between groups.
†Serious adverse events are reported that affected >1% of either group with a ratio >2.00 between groups.
‡Adverse events that led to discontinuation are reported that affected >1% of either group with a ratio >2.00 between groups.

Table IV. Serious bleeding events

Events	*Cilostazol, No (%)*	*Placebo, No (%)*
Serious bleeding events*	18 (2.5)	22 (3.1)
On aspirin	15 (2.1)	15 (2.1)
On aspirin + clopidogrel	3 (0.4)	7 (1.0)
Anticoagulated	6 (0.8)	9 (1.3)

*Serious bleeding adverse events were recorded only during treatment and ≤14 days of discontinuation of study drug; however, the timing of the serious bleeding event relative to the administration of the concomitant medication of aspirin, clopidogrel, or anticoagulants was not recorded.

verse events common to cilostazol included dyspnea, whereas serious adverse events numerically less common on cilostazol compared with placebo were cerebrovascular accidents, carotid artery stenosis, femoral artery occlusions, and cardiac arrest, although there were small absolute numbers of events in these categories. Adverse events leading to discontinuation on cilostazol included edema, headache, and diarrhea.

Rates of serious bleeding events were similar between treatment groups, affecting 2.5% of patients on cilostazol and 3.1% of patients on placebo (Table IV). Fifteen patients randomized to cilostazol who were also taking aspirin had serious bleeding events, an identical number of hemorrhages as in patients randomized to placebo who were also taking aspirin. There were no differences in serious bleeding events between groups in the patients who also were taking aspirin and clopidogrel or anticoagulants.

DISCUSSION

Cilostazol is indicated for the treatment of the symptom of claudication in patients with PAD; however, the long-term safety of this drug was not known at the time of FDA approval. This study demonstrated that all-cause mortality during drug administration was similar between cilostazol and placebo, both on-treatment and when followed up to 42 months. On-treatment, the point estimate of the hazard ratio was 0.99 and more important, the upper bound of the 95% CI was 1.88. Analysis of cardiovascular mortality gave similar results. These findings indicate no signal of safety concern with cilostazol in the population studied; however, owing to the limited number of deaths accrued, the study could not exclude a modest adverse mortality effect.

The demographics of the current population were typical of previous studies of cilostazol and other claudication drugs.[12-17] These populations have included subjects aged in their mid-60s, who were predominantly male and non-Hispanic white. The patients also had a predominance of cardiovascular risk factors that increased their risk of cardiovascular events. The mean ABI in the current study was also typical of patients enrolled in studies to evaluate claudication therapies; therefore, this study evaluated a representative population of patients with claudication at risk for cardiovascular events. In that context, the neutral effect of cilostazol on major cardiovascular events and mortality in the current study is reassuring with respect to its current clinical use.

Previous trials of claudication drugs have focused on efficacy and therefore have typically not enrolled sufficient patients to provide a full view of safety. When mortality event rates were pooled from published claudication studies, the overall mortality rate was 1.9 deaths per 100 patient-years.[18] This value is in a similar range as the all cause mortality rates in the on-treatment population in CASTLE. The mortality rates in claudication studies may be lower than previous natural history studies owing to selection bias of enrolling patients who can perform a treadmill test into a claudication study, exclusion of patients with the most serious comorbidities, and high compliance with other risk-reduction strategies. Approximately 75% of the all-cause mortality in CASTLE was cardiovascular. Although the all-cause mortality rates were apparently higher when patients were followed up longer in the ITT population, the cardiovascular rates remained relatively similar. This suggests a change in the rate of noncardiovascular deaths over time, but any change in cause-specific death over extended follow-up periods in patients with PAD would need to be confirmed.

The original concerns about mortality risk with phosphodiesterase inhibitors were raised in the placebo-controlled Prospective Randomized Milrinone Survival Evaluation (PROMISE) study of oral milrinone in 1088 patients with class III or IV heart failure followed up for a median of 6 months.[6] The study accumulated 295 deaths with a hazard ratio for mortality on milrinone of 1.28 and an upper 95% CI of 1.61 ($P = .038$). Most of the excess deaths were in patients with New York Heart Association functional class IV heart failure. This raised the concern during the FDA discussions on the approval of cilostazol that there could be a class effect for phosphodiesterase inhibitors increasing risk of death in all patients with cardiovascular disease, including PAD.[9] The excess mortality

observed in PROMISE was consistent with the overall experience with phosphodiesterase inhibitors in patients with heart failure. A meta-analysis of 8408 patients with heart failure identified that the these drugs were associated with an increased of 17% (upper 95% CI, 1.30) for all cause mortality.[19]

However, several important distinctions exist between the use of milrinone in heart failure and cilostazol in claudication. The PROMISE study evaluated a much sicker population of patients, where 295 deaths were accumulated on-treatment, in contrast with only 37 deaths on-treatment in CASTLE. The greater number of events in the PROMISE study provides more certainty in the point estimate of excess risk. Although CASTLE had many fewer events, in contrast to PROMISE, the point estimate for all-cause mortality on-treatment was 0.99. Thus, although cilostazol is a phosphodiesterase III inhibitor, no signal of increased risk was evident when used in patients with PAD without heart failure.

Adverse events were common in all patients enrolled in the study. Formal statistical testing of any adverse event outcomes between drug and placebo was not prespecified; therefore, the current adverse event rates are descriptive in nature. In that context, cilostazol was associated with headache, palpitations, and diarrhea, as previously described.[7] Serious adverse events were also similar between groups but with numerically fewer cerebral and peripheral arterial events in patients randomized to cilostazol. Adverse events leading to premature termination were also expected (headache and diarrhea), but edema as a cause of discontinuation from cilostazol has not been previously described. Of importance was that adverse bleeding events and serious adverse bleeding events were similar between cilostazol and placebo whether patients were also taking other antiplatelet or anticoagulant drugs. A previous study in patients with PAD found the addition of cilostazol to background therapy with either aspirin or clopidogrel did not further increase the bleeding time.[20] The lack of increased bleeding risk with cilostazol in patients taking other antiplatelet drugs in CASTLE is thus consistent with this previous report. Therefore, cilostazol did not appear to increase the risk of bleeding, even in patients taking background antiplatelet or anticoagulant therapy.

This study had several limitations. The anticipated number of deaths was not achieved, and thus, the study was underpowered to test its primary end point. Despite that limitation, the very neutral point estimate of the hazard ratio and the 95% CIs for all-cause and cardiovascular mortality on-treatment do exclude a clinically meaningful level of increased risk on cilostazol.

In addition, most study deaths occurred >30 days after discontinuation of the study medication. Because these deaths were unlikely to be attributable to the study drug, they could have masked any signal generated during the on-treatment period. This necessitated a post hoc change in the primary analysis to an on-treatment population that reflects actual drug exposure and therefore more accurately reflects drug risk.

The large number of dropouts from the ITT population was due to a variety of causes, but was most commonly related to withdrawal of consent, adverse events, and other factors. The patients who dropped out were well balanced between drug and placebo, particularly in the patients who terminated early for whom vital status was not known. Given the overall balance of deaths on treatment between drug and placebo, it is unlikely that the absence of information on vital status from these patients in the ITT population would have impacted the overall results.

The study also suffered from lack of a formal adjudication of fatal and serious nonfatal events. Patients with clinical evidence of heart failure were excluded, and so the results cannot be generalized to that population. Also, a number of patients were enrolled who did not have an ABI <0.90, and additional clinical criteria for the diagnosis of PAD (imaging, prior revascularization, or noninvasive laboratory) were not available. Despite that limitation, the point estimate for all-cause mortality was similar to that in the larger populations. Finally, the temporal association of a serious bleeding event to exposure to an antiplatelet or anticoagulant drug could not be ascertained.

In summary, cilostazol was well tolerated and was not associated with increased risk of mortality or bleeding. The expected side effects of headache, diarrhea, and possibly edema were observed on cilostazol.

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Data collection: Otsuka Pharmaceuticals
Writing the article: WH, EB
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Final approval of the article: WH
Statistical analysis: WH, EB
Obtained funding: WH
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Additional material for this article may be found online at www.jvascsurg.org.

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